REMARKS

Claims 1, 3-19, 27, 29-44, 52-53, 56, 58-60, and 65 are currently under examination in the application. Withdrawn claims remain in the application and are subject to rejoinder. No amendments are currently being made to the application; however, new claim 65 is being added. Claim 65 substantially parallels claim 1 except for the requirement that the water insoluble compound contains at least three polar groups. Claims 2, 28, 54-55, 57 and 61-64 were previously canceled, and claims 20-26 and 45-51 have been withdrawn from consideration. The prior sheets labeled as 'Listing of Claims" show all the claims of the application with an indication of the current status of each.

Claim Rejections

I. 35 USC § 103(a)

Claims 1, 3-19, 27, 29-44, 52-53, 56, and 58-60 stand rejected under 35 USC § 103(a) as obvious over Landh et al. (U.S. patent 5,531,925, hereafter "Landh") in view of Benet et al. (U.S. patent 5,716,928, hereafter "Benet") and Yau (U.S. patent 5,541,287, hereafter "Yau"). This rejection is traversed.

A. Summary

When properly understood, the Invention is not obvious in light of the prior art. The Invention addresses the problem of how to incorporate into reversed cubic phase or reversed hexagonal phase material certain compounds (including pharmaceutical drugs) ("drugs") which are otherwise difficult or impossible to incorporate therein. The inventor discovered that a small and identified set of compounds (generally, "co-solubilizers") may be incorporated as a fourth component of the cubic phase or hexagonal phase system enabling loadings of certain drugs unachievable without them. The addition of this fourth component permits unexpectedly high drug loadings. At the molecular level, it creates a radical structural change in the bilayer component of the lyotropic liquid crystal phase material, which in turn causes unexpected and significantly different overall structure and properties of the material, which synergistically both create a local milieu in the bilayer conducive to the drugs, and, by impacting the radius of curvature of the lipid layer, can serve promote and maintain the cubic or hexagonal phase of the composition.

B. Scope and Content of the Prior Art

1. Landh.

Landh discloses stabilized particles in dispersion comprised of a reversed cubic or reversed hexagonal phase interior incorporating a drug, and a stabilizing lamellar or L_3 phase surface coating, and methods of making and using same. [Note, hereafter throughout this filing, for brevity's sake, "cubic and hexagonal" will be referred to simply as "cubic" unless the context requires otherwise.] Landh teaches that the addition of a fragmentation agent to homogenous three component (solvent, lipid/surfactant, drug) reversed cubic phase material to liquefy a part of the cubic phase, that is, to transform the outer surface of the cubic phase material into an entirely different and distinct phase of material (either lamellar phase or L_3 phase), so as to provide a stabilizing surface coating and enable dispersion in a medium. Landh also teaches the use of high HLB (water soluble) poloxamers as fragmentation agents.

2. Benet.

Benet teaches that the co-administration of oral pharmaceuticals and certain essential oils (column 2, lines 33-43; column 3, lines 21-29) increases the bioavailability of the pharmaceutical in a mammal. Benet describes the loci of the effect of the essential oils is at the cellular level. The essential oils: (i) inhibit the enzyme Cytochrome P450; (ii) reduce Cyp3A; and/or, (iii) inhibit P-gp reflux. (column 2, lines 9-20). "Co-administration" is defined by Benet to include "concurrent administration (administration of the essential oil and the drug at the same time) and time-varied administration (administration of the essential oil at a time different from that of the drug), as long as both the essential oil and the drug are present in the gut lumen and/or membranes during at least partially overlapping times." (column 25, lines 16-22). Thus, according to the teachings of Benet, the essential oil does not even have to be administered at the same time, and thus not even in the same composition, as the pharmaceutical, in order to be effective. The use of essential oils taught by Benet is not an integral component of the composition that contains the drug, and is not described as bearing any special relationship to the drug or interacting with the drug or formulation itself. Rather, the essential oil works at the cellular site in the body. Benet is silent about the mechanism by which essential oils operate at the molecular level.

3. Yau.

Yau teaches radiolabeled small molecules for use in diagnostic or therapeutic pre-targeting methods, specifically novel radioiodinated biotin derivatives that are of relatively low molecular weight, in contrast to prior art derivatives relatively high molecular weight (column 6, lines 33-38. Pre-targeting is described in column 3 at lines 41-49 as involving target site localization of a targeting moiety that is conjugated with one member of a ligand/antiligand pair. After a time period sufficient for optimal target-to-non-target accumulation of this targeting moiety conjugate, active agent conjugated to the opposite member of the ligand/antiligand pair is administered and is bound to the targeting moiety conjugate at the target site. Thus, the method provides a mechanism for delivering an active agent into close proximity with a cellular target and prevents accumulation of active agent at non-target areas. By its very nature, the invention is applicable to many targets and consequently many actives. The target may be, for example, a tumor, and the active agent may be an anti-tumor agent. Paclitaxel is disclosed only at column 9, line 28 in a list of many possible active agents that could be conjugated to the biotin derivatives and delivered by the methods of the invention. Paclitaxel is not described by Yau as provided in a composition in which it is dissolved and certainly not in a structured fluid as is the case in the present invention. Yau also lists literally hundreds – and with permitted variations, perhaps thousands - of ingredients which are preferred or may be used in the practice of various aspects of the invention. At column 29, at lines 29-30, gentisic acid is identified in a list of antioxidants that can be used for the sole purpose of protecting the macrocyclic ring of the low-molecular weight biotin derivatives from degradation due to radiation.

C. Comparison of Prior Art to the Invention

1. The Invention

The Invention is directed at the problem of how to incorporate certain drugs which are difficult to incorporate into a reversed cubic phase or reversed hexagonal phase material; that is, how to enable the loading of drug while retaining or establishing the reversed cubic or reversed hexagonal phase, or morphology, of the material.

Reversed cubic and reversed hexagonal phase lyotropic liquid crystalline phase materials have unique and beneficial properties and behaviors in the delivery of drugs, springing from their intricate and unique morphology. Some drugs are readily incorporated at useful loadings, and partition strongly, within simple reversed cubic or reversed hexagonal phase materials composed of lipid and water. Others, indeed the majority, are not.

In a large number of cases, drugs cannot be incorporated into a binary lipid-water cubic phase at any pharmaceutically useful concentration. Lipids and other surfactants are simply of too high in molecular weight (typically 300-1,000 or more) to be powerful solvents, the likes of methanol, acetonitrile, etc., in spite of their pronounced and utilitarian amphiphilicity. Furthermore, since nearly all surfactants and lipids have (almost by definition) large apolar groups composed entirely—one might say monotonously—of hydrocarbon chains, this makes the interior of a lipid/surfactant bilayer a foreboding place for a drug molecule with polar groups scattered throughout. The Declaration of Anderson, Item 8, sets forth illustrative drugs, shows the number of polar groups in the molecule and further discusses this phenomenon.

Furthermore, because lyotropic liquid crystal phase behavior, by definition, is driven by the relative concentration of ingredients, the incorporation of one or more new components to a cubic or hexagonal phase material frequently causes a phase transition to another different lyotropic liquid crystal phase, complete with different nanoscale morphology and different characteristics and behavior.

Ready incorporation is preferable and beneficial for many reasons in the pharmaceutical field, including minimizing the amount of excipients required in the formulation, increasing concentration gradient-driven drug fluxes, and maximizing potential API loading to enable high dosing in a single administration, as well as various benefits unique to cubic phase or hexagonal phase material.

The invention identifies certain molecules, generally termed "co-solubilizers", which can be introduced as a fourth component in the cubic phase material, and which simultaneously enable higher drug loadings and maintain or establish the cubic phase of the material. Specifically, the Invention provides compositions comprising a structured fluid and a compound present in the structured fluid, the compound being less than 5% by weight soluble in soybean oil or being water insoluble and containing at least three polar groups. The structured fluid comprises three elements: 1) a polar solvent (e.g., water); 2) a lipid or surfactant (e.g., a poloxamer, or phosphatidylcholine); and 3) a "co-solubilizer", that is, an essential oil or dissolution/solubilization agent or both (such as spearmint oil or gentisic acid). The compound present in the structured fluid may be a pharmaceutical drug, such as paclitaxel.

2. Landh.

The Landh reversed cubic phase material is substantially a three component system – solvent, lipid/surfactant and drug. In contrast, the Invention teaches a four component cubic

phase material – solvent, lipid/surfactant, drug and co-solubilizer. (See the Declaration of Anderson, Item 10 for this and following discussion.)

Landh does teach a fourth component of the invention, but for an entirely different purpose and effect than in the Invention. Landh's fourth component, termed a "fragmentation agent", is introduced to partially liquefy the reversed cubic phase material; that is, to cause a phase change away from cubic or hexagonal phase toward lamellar or L_3 phase material. As a direct result of the addition of the fragmentation agent, this material of a "distinct" lamellar or L_3 phase is created and encircles the reversed cubic phase or reversed hexagonal phase material core, creating in dispersion stabilized particles (i.e., the three component cubic phase material is present inside a lamellar or L_3 phase coating, and the coating aids in dispersion of the particles.)

By contrast, the Invention teaches a four component cubic phase: solvent (e.g., water); lipid/surfactant (e.g., poloxamer [low HLB, water insoluble]); drug (e.g., paclitaxel); and co-solubilizer (e.g., spearmint). In the Invention, the fourth component is incorporated in the cubic phase, and plays the key role of increasing the amount of drug that is incorporated into the cubic phase while at the same time contributing to the maintenance or establishment of the cubic phase nature of the material.

In Landh, the fourth component is not essential for the existence of the cubic phase, but rather is present for its partial destruction, transforming it to lamellar or L_3 phase, distinct from the cubic phase material, and with a new property of coating and stabilizing the cubic phase material. By contrast, in the Invention the co-solubilizer is an essential element of the four component cubic phase. Without the fourth component, either the cubic phase would not form at all, or it would form but with only with significantly lower levels of incorporation of the drug. The co-solubilizer also promotes and maintains the cubic phase morphology of the material..

The addition of Landh's fragmentation agents to transform the morphology of some of the reversed cubic or reversed hexagonal phase material to lamellar or L_3 – is the direct opposite of the effect of the addition of the co-solubilizers of the Invention. Adding co-solubilizers of the Invention moves the material from L_3 or lamellar phase toward reversed cubic or reversed hexagonal phase. As a consequence, the co-solubilizer of the Invention would inhibit the formation of the Landh particle. Conversely, use of a Landh fragmentation agent in the Invention would reduce the incorporation of the drug and tend to destroy the cubic phase material, as its expressed purpose at the heart of Landh is to induce a transformation *away from* the cubic phase: either reversed cubic → lamellar, or reversed cubic → L_3. The purpose, and

practice, of the Landh invention is thus antithetical to the Invention.

As the Examiner notes, poloxamers are identified in both Landh and the Invention, however, rather than reflecting a similarity, this shines a light on the fact that Landh and the Invention teach very different, and critical, functions and effects. In Landh, poloxamers are fragmentation agents, added for the purpose of liquefying part of the cubic phase to form a lamellar or L_3 phase material coating. For this reasons, water soluble poloxamers are preferred; in fact, poloxamers with HLB >15 are called for. (Column 10, Lines 35-37) By contrast, in the Invention poloxamers are identified as the lipids/surfactant component (for example, phosphatidylcholine is another) which forms the bulk of the bilayer, the major structural element of cubic phase material. Because this is their function in the Invention, water insoluble poloxamers (low HLB) are called for. To illustrate the immense difference in purpose, function and effect of poloxamers in the two disclosures, the use of a Landh identified poloxamer (HLB > 15) as the sole lipid/surfactant component of either the Landh reversed cubic phase particle or the reversed cubic phase of the Invention would be futile - a reversed cubic phase would not even be created. Declaration of Anderson, Item 10.

In Landh, it is of course the lipid / water cubic phase that solubilizes the drug. Yet the monoglyceride / water cubic phase of the Examples has limited capacity to take up oils or hydrophobic drugs. This tends to focus the teaching of Landh to water-soluble drugs such as biopharmaceuticals. By contrast, the Invention focuses on revamping the composition of the cubic phase with co-solubilizers so as to allow cubic phase solubilization of hydrophobic, water-insoluble drugs. Moreover, the very teaching that a lipid bilayer is, in its interior, simply a hydrophobic milieu, reflected in Landh and the others in the field, teaches away from the Invention which, at its heart, includes the new and surprising teaching that this "hydrophobic" interior can be made amphiphilic by the addition of certain compounds while retaining the desired liquid crystal ordering. Landh does not identify, let alone address, the problem of drugs with no or limited loading into reversed cubic phase or reversed hexagonal phase material. Landh does not the relative solubilization or concentration of various drugs in his material. The compounds which are identified in the Invention as difficult-to-solubilize in reversed cubic phase material are not separated out or characterized in Landh. The co-solubilizers which are identified by the Invention as the solution to the problem are not identified at all. Landh contains no mention of spacing in the bilayer, or the polar identity of a drug which form the molecular mechanism of the Invention.

3. Benet

Benet teaches the use of essential oils only insofar as they have an impact on cellular uptake of drug through the very detailed P-gp efflux, Cyp3A, Cytochrome P450 mechanisms. The test for determining which essential oils can be practiced rests on cellular uptake in an in vivo cell culture. Even in this limited respect, Benet offers no molecular level explanation of how essential oils do so.

Benet does not mention the solubility or concentration of drug in payload or structure of the delivery vehicle. Benet does mention the co-administration of an essential oil with a drug. However as taught by Benet has nothing to do with the *incorporation* of an active pharmaceutical compound (e.g. paclitaxel) in an essential oil -rich structured fluid where the essential oil is by design, and by necessity, in direct contact with the active in the formulation, as is the case in the present invention. There is nothing in Benet that teaches or suggests solubilization of an active within a structured fluid that contains an essential oil. Applicant notes that the only appearances of the terminology or concepts of "solubilization" and "dissolution" in Benet are in connection with the dissolution of the essential oil itself for purposes of applying the oil to a cell culture test (column 28 lines 22-23; column 29 lines 61-65; and column 30 lines 6-8), the classification of drugs as to the relative solubilities in octanol or water (column 16 lines 38-41), or the dissolution of a formulation in the body after ingestion (column 26 lines 52-59).

4. Yau

Yau teaches the chemical modification of drugs by conjugation to a targeted biotin derivative in order to direct the conjugate to a targeted cellular site of action, so as to improve the performance of an administered active agent.

This approach teaches away from the Invention, since the Invention is focused on the solubilization of drugs in their existing form, without chemical modifications that can greatly prolong the process of approval and acceptance of a drug. Indeed, if the invention of Yau were applied to paclitaxel, the final drug formulation would not have paclitaxel per se as an ingredient, in solubilized or any other form.

Paclitaxel is not described by Yau as provided in a composition in which it is dissolved and certainly not in a structured fluid as is the case in the Invention.

Gentisic acid appears on a list of antioxidants which are potential radioprotectants for use in practice of the invention, that is, a compound that will protect and stabilize the radiologically sensitive macrocyclic ring of the low-molecular weight biotin derivatives of the invention of

Yau. Gentisic acid is neither shown nor suggested as relevant to the solubilization of paclitaxel (or any other substance) in any way. Gentisic acid is not shown or suggested as a component of a structured fluid of any type, as is the case in the present invention. Yau is silent as to the use of structured fluids for the solubilization of drugs. Gentisic acid is taught only as a radioprotectant, and because it is an antioxidant. There is no expressed need for an antioxidant in Landh, Benet or the Invention. Nor is there any indication that a chemical structure which is capable of being protected by gentisic acid from degradation by radiation, such a macrocyclic ring which is the precise focus of Yau, is present in Landh, Benet or the Invention.

Yau lists literally hundreds – with permitted variations, perhaps thousands - of ingredients which are preferred or may be used in the practice of the invention. Like the use of gentisic acid to prevent the degradation of macrocyclic ring of a biotin derivative, all of them are completely unrelated to the problem faced or the materials being used by the Invention.

D. Evaluation of obviousness, rationale and motivation

The Examiner concludes that a prima facia case of obviousness has been made because Landh teaches the delivery of drugs using cubic phase material, and it would have been obvious to combine Landh with an essential oil because Benet "indicates that essential oils increase the bioavailability of oral pharmaceuticals when co-administered." The Examiner also concludes it would have been obvious to combine Landh and gentisic acid "because it is taught by Yau is being radio protectant." Applicant respectfully submits that on a proper understanding of the Invention and the teachings (as opposed to laundry lists of ingredients) of the prior art references, it is clear that the Invention is not obvious in light of the prior art.

The problem faced and solved by the Invention is how to incorporate certain difficult-to-solubilize drugs into certain reversed cubic phase systems. There is nothing in the problem faced by the Invention that would have brought attention to prior art which teaches increased bioavailability through inhibiting P-gp efflux at the cellular level, or protecting macrocyclic rings from oxidation due to radiation.

Landh did not identify or approach the problem of limited loadings, the goal of increased loadings, or any route to a solution.

Landh's central teaching teaches away from the Invention. Land's fragmentation agent is a fourth component introduced for the opposite purpose of the Invention, namely, to liquefy or transform part of the cubic phase material and create a lamellar or L_3 phase outside coating on

cubic phase material to form a dispersible particle. The Invention seeks to maintain the cubic phase of the material while incorporating additional drug loading.

The existence of art describing the co-administration of essential oils to suppress complex cellular systems in vivo so as to increase bioavailability does not suggest the direct incorporation of essential oils into complex structured fluid formulations. Though Benet lists dozens of essential oils, Benet did not discover essential oils, nor their many known previous uses, for example their widespread use as flavorings. Benet's teaching is that they can be used to interfere with certain cellular activity so as to increase *in vivo* bioavailability. Benet does not discuss - or even hypothesize - the molecular mechanism of action, or the characteristics of the essential oils which might cause such interference in the specific cellular systems he identifies, or another chemical or biochemical system. Benet is well known to hold other patents which identify other agents as acting on p-Gp, Cyp 31 and Cytochrome P450 cellular mechanisms. There is nothing in Benet to suggest essential oils over any of these other compounds.

Similarly, there is nothing in the teachings Yau which would suggest the use of a targeting biotin derivative conjugate in a reversed cubic phase drug delivery system, or of gentisic acid in a system with no macrocyclic ring or other identified need for protection against oxidation or radiation. Neither Landh nor Benet (or a hypothetical combination of the two) involves the use of radiation, or refers to the need for radioprotection of the components of any compositions described therein. There would therefore be no motivation to combine gentisic acid as taught by Yau with the compositions taught by Landh and Benet. Landh and Benet do not identify the need or use of compounds with radiosensitive macrocyclic rings, or any other component that would benefit from the protection of an antioxidant.

The Examiner states that since Landh is also directed at delivering cancer therapeutics, one of ordinary skill in the art would expect that the incorporation of essential oils would have "at least an additive effect" in terms of drug delivery. In fact, the attempted incorporation of essential oils into the Landh invention as a general matter would tend to destroy the cubic phase material and particles of the Invention, resulting in a negative, rather than additive, effect in terms of drug delivery. See the Declaration of Anderson, Item 9. As discussed above, Landh's essential teaching - to add a fragmentation agent to a three component cubic phase system to liquefy part of the cubic phase material and create a distinct lamellar or L_3 outer phase – moves the phase transition in one direction, from reversed cubic to lamellar or L3. The addition of essential oils moves it in the opposite direction. The monoolein-water cubic phase that is the

basis of virtually all the Examples in Landh is not capable of taking up significant levels of essential oils and maintaining homogenous cubic phase morphology. When an essential oil is added to this cubic phase, either the cubic phase is liquefied by the oil or the cubic phase imbibes a few percent, and the rest splits out as an excess oil-rich liquid phase or some other distinct lyotropic liquid or liquid crystalline phase. This monoolein-water cubic phase is well known to be very sensitive to liquefaction due to the action of even small amounts of hydrophobic liquids, low-MW solvents, etc. Many commercially sourced grades of monoolein are not able to form a cubic phase with water due to impurities. Because it is prone to liquefaction it can be expected that a large number of essential oils liquefy it. Since the particles of Landh require a reversed cubic or reversed hexagonal phase liquid crystal at the core, liquefaction destroys the particles of the Landh invention. Moreover, the addition of an essential oil also would tend to destroy the "surface phase" coating of the Landh particle, destabilizing it. This follows from the fundamentals of lipid phase behavior that addition of a water-insoluble, low-MW liquid, such as an essential oil, will tend strongly to induce a lamellar to reversed cubic phase transformation, which as discussed above is seen in the Invention. Since the surface phase of Landh is either a lamellar phase or the closely related L_3 phase, with the addition of an essential oil this surface phase will tend to convert back to a reversed cubic phase, thus destroying the coating phase that was created by a reversed cubic to lamellar (or reversed cubic phase to $L_{3)}$ transformation away from the cubic phase caused by the introduction of the fragmentation agent in the first place. Alternatively, in Landh particles where the surface phase is an L_3 phase, addition of essential oil to this partially-structured liquid phase could readily liquefy the phase to an ordinary L_2 phase, which is either a reversed micellar solution or a structureless liquid. The L_3 phase is well known to have a narrow range of existence both in terms of temperature and composition, and its characteristic bilayer structure is easily broken down.

The combination of ingredients used in the Invention, which were individually and separately identified but not taught in Landh, Benet and Yau, create a material with startling properties, unexpected in light of the prior art.

At the molecular level, this unexpected result is produced by an unexpected mechanism. See the Declaration of Anderson, Item 7. The co-solubilizer becomes a new structural element, like a spacer or "wedge", locating in the bilayer of lipid/surfactant. One effect of the wedge is to push apart the tails of the lipid/surfactant molecules and insert more polar, lower molecular weight co-solubilizer molecules. This permits association of these polar groups with drug

molecules, and thus induces certain drugs into more and closer association with the bilayer. This is particularly effective with respect to the "schizophillic" molecules described above. Another and simultaneous effect of the wedge behavior of the co-solubilizer molecules is to increase the radius of curvature of the lipid layer, or bilayer. This is the parameter which ultimately determines the phase behavior of the material – lamellar, cubic, hexagonal, etc. By the coincident and synergistic combination of these two effects from the introduction of a single component, the Invention allows the balancing required to achieve higher levels of incorporation of drug while maintaining or establishing the cubic phase.

By no means are all fourth components which are acceptable for use in drug delivery suitable for this use. As a result of extensive experimentation, the inventor found that certain insoluble molecules could be incorporated into a four component cubic phase system, while both maintaining the cubic phase and enabling the incorporation of certain drugs at higher loadings. Many common pharmaceutical ingredients have the opposite effect from what is pursued in the Invention, and destroy the cubic phase or decrease drug loadings. Others simply cannot be incorporated into a four component cubic phase system – they precipitate out, or form a liquid phase. Others bind with the drug itself and prevent its incorporation into the cubic phase material.

The inventor performed experiments with scores of pharmaceutical excipients and adjuvants, in hundreds of different combinations, in attempting to find a means of incorporating difficult to incorporate drugs into the cubic phase system. The inventor was guided in part by in-depth knowledge of molecular packing in reversed liquid crystal systems [see, e.g., P. Strom and D.M. Anderson (1992) Langmuir 8:691; D. M. Anderson, S. M. Gruner and S. Leibler (1988) Proc. Nat. Acad. Sci. 85: 5364; D. M. Anderson, H. Wennerström, U. Olsson (1989) J. Phys. Chem. 93:4532]. The extensive experimentation led to the surprising result that essential oils—accepted as pharmaceutical excipients largely for their history of used as flavor and fragrance agents—along with a small handful of identified solubilization agents, including tocopherol, succeeded where a wide range of other excipients failed. Their incorporation led to a four component cubic phase system in which solubility of the drug in the cubic phase increased dramatically – as compared to in oil or water, and in comparison to the cubic phase without the co-solubilizer, and the cubic phase nature of the material could be maintained.

On examination, the co-solubilizers share structural characteristics, which appear to

permit the behavior in the bilayer described above: (i) an uneven distribution of polar and apolar groups along the molecular backbone; (ii) a low molecular weight (relatively smaller molecule); and (iii) a relatively high partition coefficient. The use of these co-solubilizers creates a radically different and consequential physiochemical change at the molecular level of the bilayer component of the cubic phase, which impacts the overall structure and properties of simple lipid-water mixtures in ways unexpected in light of the prior art, principally allowing the incorporation of otherwise difficult to incorporate drugs in reversed cubic phase material, which is of great utility in the field of pharmaceuticals.

A further illustration of the surprising results of the two coincident molecular level effects of the Invention is the case where the lipid component is phosphatidylcholine, perhaps the most widely accepted lipid or surfactant in pharmaceutics. Phosphatidylcholine-water binary systems form lamellar phase liquid crystal at ambient temperature, as well as body temperature. Thus, alone it is of limited use in cubic phase technology, unless combined with another lipid, many of which would be less widely accepted in pharmaceutics. However, as noted throughout the Invention disclosure, many of the identified co-solubilizers, such as essential oils and tocopherol, increasing drug loading and simultaneously inducing the formation of reversed cubic phase in phosphatidylcholine-water mixtures.

Similarly, the use of gentisic acid in the present invention results in a synergistic combination of a sufficiently high partition coefficient (making it bilayer-associated) and strongly polar groups, such that the compound not only strongly improves the polar characteristics of the surfactant bilayer in the structured fluids of focus, but also can be used to modulate the phase behavior of the surfactant system to achieve a desired liquid or liquid crystalline phase.

The Declaration of Anderson, Item 5 confirms that a three component cubic phase material of poloxamer identified in the Invention, water and paclitaxel simply cannot be produced. The paclitaxel is insufficiently solubilized and precipitates out. The loading of the paclitaxel in the cubic phase is negligible. With the addition of spearmint oil, however, a four component cubic phase system is created which has significant drug loadings.

The Table set forth in the Declaration of Anderson, Item 6, shows the comparative solubility of various drugs using the Invention to incorporate the drug into the cubic phase, as compared to solubility in oil and water. The increase in drug incorporation is at least one and in some cases several orders of magnitude greater. The Declaration establishes that these PC –

water – drug systems form and incorporate significant drug loadings, when in the absence of the co-solubilizer the drugs could not even be incorporated into the cubic phase system. With the co-solubilizer tocopherol, they form cubic phase material, and do so at very high levels of solubilization comparative to other systems.

As discussed in the Invention disclosure, reversed cubic phase and hexagonal phase material with effective drug loadings is of significant pharmaceutical utility - minimizing total excipient load and enabling a greater dose delivered per administered unit with the unique benefits of the reversed cubic phase or hexagonal phase formulation system springing from their intricate and unique morphology and the properly balanced compositions that give rise to this morphology.

II. Obviousness Double Patenting - US Patent Application Ser. No. 10/460659.

Claims 1, 3-19, 27, 29-44, 52-53, 56 and 58-60 stand (provisionally) rejected on the grounds of non-statutory obviousness-type double patenting as unpatentable over claims 1-7, 9-15, 17-36, 38-39 and 74-75 of co-pending US patent application 10/460,659, in view of Yau et al.

In order to accelerate prosecution, with the understanding that Applicant disputes the finding, Applicant herewith submits a terminal disclaimer to disclaim the patent term of any claims from the present application which issue in a patent, so that the patent term of such claims would expire at the same time as that of a patent which issues for claims 1-7, 9-15, 17-36, 38-39 and 74-75 of copending US patent application 10/460,659.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

III. Obviousness Double Patenting - US Pat No. 6,991,809

In order to accelerate prosecution, with the understanding that Applicant disputes the finding, Claims 1, 3-19, 27, 29-44, 52-53, 56 and 58-60 stand rejected on the grounds of non-statutory obviousness-type double patenting as unpatentable over claims 1-84 of US patent 6,991,809.

Applicant herewith submits a terminal disclaimer to disclaim the patent term of any claims from the present application which issue in a patent, so that the patent term of such claims would expire at the same time as that of claims 1-84 of US patent 6,991,809.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

IV. New claim 65

Support for new claim 65 can be found on page 32, and in Table 1 on pages 32-34 of the application. Table 1 lists representative pharmaceutical compounds from some of the major therapeutic categories which are of low solubility in water (a fraction of a percent solubility), and tabulates the number of polar groups on the molecule. The table demonstrates that many, if not most, water-insoluble drugs contain at least 3 polar groups, and would be expected to have low solubility in a simple lipid-water mixture. The incorporation of a dissolution/solubilization agent in accordance with the present invention remedies this. Examination of the chemical structure of each of these compounds furthermore reveals that the polar groups are spread throughout the molecule, so that only in rare cases would the molecule be able to situate itself in a simple (lipid-water) bilayer with an orientation analogous to that of a surfactant. Most of these drugs listed are also problematic when attempts are made to solubilize the drug in water by converting the drug to a salt, such as a hydrochloride, or sodium salt for example; for example, some would precipitate at the pH of the body milieu, others would decompose, etc.

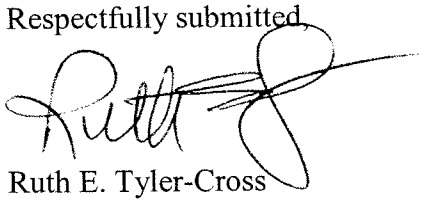
Conclusion

In view of the foregoing, it is requested that the application be reconsidered, that claims 1, 3-19, 27, 29-44, 52-53, 56, 58-60 and 65 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; email: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview.

If an extension of time is required for this response to be considered as being timely filed, a conditional petition is hereby made for such extension of time. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



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